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Local, integrated control of blood flow Professor Tudor Griffith Memorial

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ABSTRACT

Professor Tudor Griffith was one of the founding members of the European Study Group on Cardiovascular Oscillations, and hosted the 1st ESGCO Conference in Cardiff, Wales in 2000. Tudor was a passionate scientist, who managed to combine his enthusiasm for vascular biology with his background in physics, to make key and insightful advances to our knowledge and understanding of the integrated vascular control mechanisms that co-ordinate blood flow in tissue perfusion. He had a particular interest in the endothelium, the monolayer of cells that lines the entire cardiovascular system and which is in prime position to sense a wide variety of modulatory stimuli, both chemical and mechanical.

Over the last 20 years Tudor produced a series of research papers in which he used chaos theory to analyse the behaviour of arteries that underpins vasomotion. The research led to the development of mathematical models that were able to predict calcium oscillations in vascular smooth muscle with a view to predicting events in a complete virtual artery.

This article will review the field in which he worked, with *an obvious* emphasis on his contribution.

1. Vasomotor control

1.1. Local regulation

Under basal conditions arterial smooth muscle exhibits some degree of contraction, a feature that determines the tone and diameter of the vessel; in the absence of such tone cardiac output would be insufficient to maintain the circulation (Bevan and Laher, 1991). Additionally a level of basal tone enables a vessel to respond to stimuli, to vasodilate allowing increased localised blood flow and tissue perfusion, such as that required by increased metabolic demand. Vasodilation can be considered to be a loss of tone, as it is a function that is reliant on basal vascular tone which varies between vessel type, dependent on the requirements of the tissue or organ being perfused by the vessel. Vascular tone is controlled by a balance between competing vasoconstrictor and vasodilator influences determined by a variety of extrinsic and intrinsic control mechanisms.

Extrinsic factors originate from outside the tissue in which the blood vessel is located. Examples of extrinsic control mechanisms include circulatory hormones such as angiotensin II, and neuromodulatory control by neurotransmitters such as catecholamine released from sympathetic perivascular nerves and acting through adrenoceptors on vascular smooth muscle cells (Burnstock, 1993). Intrinsic factors originate within the blood vessel and include those inherent to smooth muscle cells (myogenic mechanisms), factors released by the endothelium and from the surrounding tissue, (such as by-products of tissue metabolism and other biochemical pathways). Many organs thus have an innate ability to influence and maintain their own blood supply via intrinsic factors, a mechanism termed “local regulation”. The intrinsic mechanisms responsible for local regulation act independently of extrinsic control, and can therefore be demonstrated in isolated organs, a situation in which there is no neural or hormonal influence.

1.2. Vascular smooth muscle contraction, myogenic tone

The mechanisms by which intrinsic factors influence blood vessel tone involve a variety of signal transduction mechanisms, all of which ultimately influence the regulation of cytosolic free Ca^{2+} $[Ca^{2+}]_i$ within the smooth muscle, and activation of the contractile machinery. Calcium combines with calmodulin and the complex formed interacts with myosin light chain kinase (MLCK) an enzyme that phosphorylates myosin light chain, thereby permitting interactions with actin and triggering the cycling of myosin crossbridges along the actin filaments with the development of force (Hill et al., 2001).

The chain of processes linking a stimulus to the contractile response of a muscle is known as excitation–contraction coupling (EC) and two major types have been described in vascular smooth muscle, namely electromechanical and pharmacomechanical. Fluctuations in $[Ca^{2+}]_i$ during electromechanical coupling depend on changes in the membrane potential of the cell. Depolarization of the plasma membrane induces the opening of voltage operated (L-type) Ca^{2+} channels (VOCs), allowing the influx of Ca^{2+}. Hyperpolarization, predominantly through the opening of potassium channels, closes VOCs. Pharmacomechanical

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coupling is initiated through receptor occupation by agonists promoting activation of plasmalemmal receptor operated Ca^{2+} channels, or generation of the second messenger inositol 1,4,5-trisphosphate ($InsP_3$) and Ca^{2+} release from the main intracellular Ca^{2+} store, the sarcoplasmic reticulum (SR), via stimulation of the $InsP_3$ receptor (Guibert et al., 2008). Ca^{2+} release from the SR is also mediated through the mechanism of Ca^{2+} induced Ca^{2+} release (CICR) via ryanodine sensitive Ca^{2+} release channels (RyR) (Hill-Eubanks et al., 2011).

1.3. Myogenic mechanisms

Smooth muscle cells are effectively in a continuous state of activation and this is partially due to the myogenic response, a mechanism that originates in the smooth muscle of blood vessels and is particularly pronounced in small arteries and arterioles. When the lumen of a blood vessel is suddenly expanded, as occurs when intravascular pressure is suddenly increased, the tension in the wall of the vessel also increases, this leads to Ca^{2+} entry through stretch activated voltage-dependent and -independent mechanisms and activation of the contractile proteins, this is the myogenic response (Hill et al., 2001). These events are likely supported by a number of other mechanisms, including the rearrangement of cytoskeletal elements, Ca^{2+} release from the SR and increased Ca^{2+} sensitivity of the contractile elements. The myogenic response can be regarded as unstable positive feedback and can spread to adjacent segments of the same vascular network with the potential for uncontrolled vasoconstriction and instability in the intact circulation. Negative feedback is provided in smooth muscle by the rise in Ca^{2+}, promoting Ca^{2+}-sensitive potassium channel (K_{Ca}) activation leading to hyperpolarization, and through cross talk with the endothelium (Hill et al., 2001).

1.4. Endothelium and autoregulation

In 1980 Furchgott and Zawadzki established the endothelium as a key modulating influence on vasodilatation. They discovered that stimulation of muscarinic receptors on endothelial cells stimulated the release of a mysterious endothelium-derived relaxing factor (EDRF), that caused potent relaxation of vascular smooth muscle. EDRF was shown to be labile diffusible factor, with a half-life of around 6 s (Griffith et al., 1984), with its production dependent on extracellular calcium (Griffith et al., 1986). The vascular smooth muscle relaxation by EDRF was predominantly through activation of the enzyme soluble guanylate cyclase and the formation of the second messenger cyclic nucleotide cyclic guanosine monophosphate (cGMP) (Rapoport and Murad, 1983; Griffith et al., 1985). cGMP-mediated effects include, Ca^{2+} desensitization of myosin activity (Somlyo and Somlyo, 2003) and a reduction in the $[Ca^{2+}]_i$ available for contraction through a number of mechanisms (Griffith, 1994; Francis et al., 2010). In 1987 it was established that EDRF was nitric oxide (NO) (Palmer et al., 1987), formed in the endothelium from its precursor L-arginine, by the calcium sensitive constitutive enzyme endothelial Nitric Oxide Synthase (eNOS) (Bredt and Snyder, 1990).

The agonist stimulated rise in endothelial $[Ca^{2+}]_i$ required to activate eNOS is biphasic. An initial rise in $[Ca^{2+}]_i$ from $InsP_3$-sensitive endoplasmic reticulum (ER) stores, is followed by a sustained elevation mediated by Ca^{2+} influx through activation of the capacitative Ca^{2+} entry pathway that follows depletion of the ER Ca^{2+} store (Sedova et al., 2000). In addition to pharmacological stimulation, NO is continuously released in the basal state (Griffith et al., 1987a), and the endothelium responds to hemodynamic forces such as shear stress and stretch and release of NO is sensitive to flow velocity, viscosity and pulsatility (Hutcheson and Griffith, 1991). Shear forces are sensed by multiple mechanotransducer molecules, the cytoskeleton and membrane components that transmit the signal into the interior of the endothelial cells. The event triggers a variety of cellular responses through stretch-activated channels and activation of G proteins that elevate $[Ca^{2+}]_i$ within seconds (Hutcheson and Griffith, 1997; Balligand et al., 2009). In addition to being a potent vasodilator NO also has other actions on the vasculature. NO: has antithrombotic actions, inhibits platelet aggregation and leucocyte adhesion and penetration; prevents proliferation of vascular smooth muscle cells; prevents the formation of oxidised low-density lipoprotein cholesterol (LDL) (Moncada et al., 1991, Vanhoutte et al., 2009). Consequently, a reduction in bioavailability of NO, as in the case of increased reaction rates with the superoxide anion under conditions of oxidative stress, leads to pathological disorders such as atherosclerosis (Napoli et al., 2006).

1.5. NO and flow in vascular networks

Griffith and colleagues developed techniques using X-ray microangiography that allowed simultaneous imaging of vessels of different sizes in an isolated, yet intact, vascular bed. The technique was especially suited to study responses to changes in flow in the presence and absence of NO activity (Griffith et al., 1987b, 1988; Randall and Griffith, 1993). NO-mediated dilatation to flow was shown to co-ordinate changes in calibre throughout the vascular bed, illustrating the interdependence of vessels and emphasising the need to consider integrated behaviour as a whole. The endothelium was shown to confer stability by superimposing an opposing feedback mechanism to the myogenic response within the smooth muscle, thus preserving constancy of flow distribution at different flow rates to prevent vascular "steal" (Griffith and Edwards, 1990a). Studies on the distribution of flow at arterial bifurcations suggested that, over a wide range of flow, basal NO activity maintained geometrical optimality in terms of minimum volume and power losses, helping to minimise cardiac work by allowing rapid changes in flow to occur with only small changes in central arterial pressure (Griffith and Edwards, 1990b).

Microcirculatory control should ultimately serve to match organ perfusion to metabolic requirements. Stabilizing mechanisms such as autoregulation, maintenance of flow distribution, and limitation of cardiac work relative to perfusion are important considerations for overall cardiovascular function. By modulating local vascular tone in response to the integrating signal of blood flow through NO, the endothelium couples changes in resistance in different parts of the vascular bed and thereby contributes to the co-ordination of all local control mechanisms. NO also participates in the regulation of flow through feedback loops that involve extrinsic factors such as neurogenic mechanisms of vascular regulation. Under conditions of sympathetically-mediated arterial constriction, shear forces will increase and the resultant enhancement of NO synthesis may exert inhibitory prejunctional effect on catecholamine release and diminish the original constrictor stimulus (see Griffith, 1994 for review). Thus any impairment of NO activity will have adverse effects on its important physiological role in maintaining "efficiency" of perfusion.

2. Vasomotion

Vascular smooth muscle is often observed to undergo "spontaneous" rhythmic contractile activity that leads to oscillations in vascular diameter, a phenomenon known as vasomotion (Pradhan and Chakravarthy, 2011). Vasomotion can be seen in many, if not all, vascular segments, it occurs both in vivo and in vitro, and is generated from within the vascular wall so that it is not a consequence of the heart beat, respiration or neuronal input (Aalkjaer and Nilsson, 2005). Although the physiological significance of vasomotion remains the subject of ongoing debate, it is widely assumed that the local fluctuations in tissue perfusion confer an advantage over steady-state flow. At the simplest functional level, by continuously redistributing flow, vasomotion will ensure that all tissue elements ultimately receive perfusion. Indeed, in pathological states such as haemorrhagic shock, vasomotion becomes particularly